REMARKS

I. Status of the Claims

Claims 1-29, 31 and 32 are pending and stand rejected. Claim 31 has been amended to incorporate the limitations of claims 33 and 34, which are cancelled herein.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 31, 33, and 34 have been rejected under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for a method of treating certain cancers such as breast, ovarian, colorectal, prostate, and lung cancer, does not reasonably provide enablement for a method of treating all proliferative disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." Office Action at 2.

Without prejudice or disclaimer, and solely to expedite prosecution, claim 31 has been amended to recite that the anti-proliferative effect treats a cancer chosen from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head, neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine, and vulval cancers.

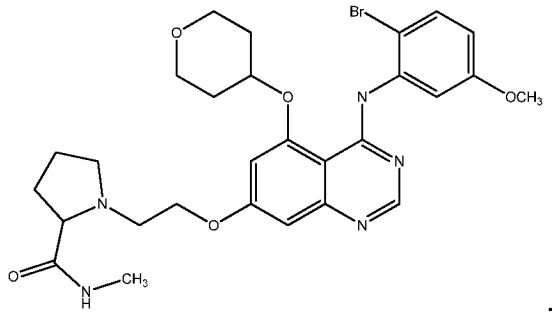
Applicants respectfully submit that the subject matter of claim 31 as amended is enabled by the specification as originally filed. Accordingly, withdrawal of the present rejection is respectfully requested.

III. Rejection Under 35 U.S.C. § 103

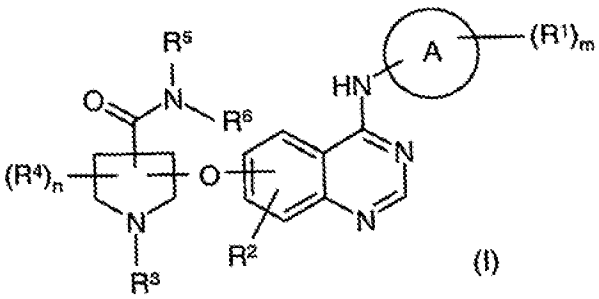
Claims 1-29 and 31-34 are rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 7,160,891 ("Moore") in view of U.S. Patent No. 5,962,458 ("Lohmann").

The Rejection

As a starting point for the rejection, the Office references the compound recited at column 47, lines 34-36 of Moore, i.e., 4-(2-bromo-5-methoxyanilino)-7-{2-[(2S)-2-(N-methylcarbamoyl)pyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4yloxyquinazoline ("the Moore Compound"), which has the following structure:



The Office asserts that the Moore Compound is analogous to instant formula I



wherein:

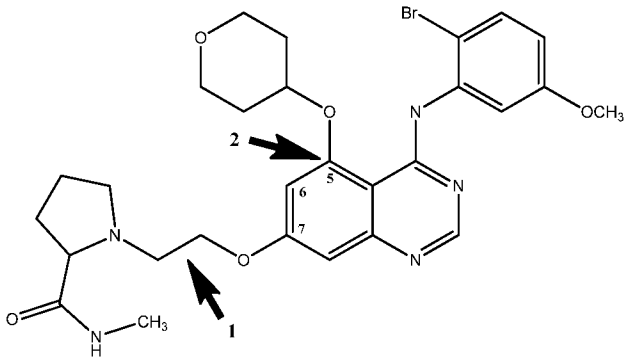
A is phenyl;
R^1 is alkoxy and halogen; m = 2;
R^3 is hydrogen; n= 0;
R^4 does not exist;
R^5 and R^6 are alkyl.[1]

[1] As discussed further below, that is incorrect. First, in the Moore Compound, R^3 of formula (I) would not be hydrogen. Rather, it would be absent since the nitrogen of the pyrrolidinyl ring of the Moore

The Office concedes that the Moore Compound differs from those within the scope of the present claims, specifically by:

(1) having an *alkylenyl-O-* chain between the pyrrolidinyl ring and the phenyl ring of the quinazoline [shown at position **1** in the diagram below], not a direct -*O*- link as required by the present claims, and

(2) having a substituent (specifically, the tetrahydropyran-4-yl-oxy group) at the 5-position of the quinazoline ring [shown at position **2** in the diagram below], not at the 6-position as required by the present claims. Office Action at 7.



However, in the Office's opinion, those two differences "can be remedied by the teaching of Lohmann". *Id.* Specifically, the Office points to column 2 of Lohmann which discloses a quinazoline derivative substituted at the 6- and 7- positions and alleges that "[t]he substituent at the 7-position is R^4-Y^1-, wherein Y^1 can be -O-, and R^4 is a heterocyclic group which could be substituted with -C(O)-$NR^{12}R^{13}$." *Id.*

The Office concludes that "one skilled in the art would have been motivated to place the *pyrrolidinyl* ring directly linked to the *oxygen* (i.e., *pyrrolidinyl-O-)* because

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Compound is bonded to an ethoxy linkage. Second, in the Moore Compound, one of R^5 and R^6 would be hydrogen and the other would be an alkyl (specifically a methyl) group.

such a modification would have maintained the same biological activity for the compound as VEGF inhibitors." *Id*.

Applicants respectfully traverse this rejection.

Applicants' Remarks

The Office has not provided a single reason why one of ordinary skill would have selected the Moore Compound as a lead compound. The Office also has not shown that the art would have suggested making either of the two proposed modifications to the Moore Compound. The art, in fact, would not have suggested making either of those modifications but would have taught away from doing so. Finally, even if the Moore Compound were modified in the manner proposed by the Office, the modified compound still would not have met all of the limitations of the present claims.

A Reasoned Identification of a Lead Compound is Required But Has Not Been Made

The Office has not proffered any reason why one of ordinary skill would have selected "the Moore Compound," discussed above, as a starting point for modification. Following *KSR Int'l* Co. *v. TeleFlex Inc.,* 127 S.Ct. 1727 (2007), the Federal Circuit has made clear that, "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the **reasoned identification of a lead compound**" in the art. *Eisai* Co. *Ltd. v. Dr. Reddy's Labs.,* Ltd., 533 F.3d 1353, 1357, 87 U.S.P.Q.2D (BNA) 1452 (Fed. Cir. 2008) (emphasis added).

In the present case, Moore discloses thousands of different compounds. However, the Office has not provided a single reason why one of ordinary skill would have selected the Moore Compound as a lead compound from those thousands of

different compounds. Accordingly, for at least this reason, Applicants respectfully assert that a prima facie case of obviousness has not been established and request withdrawal of the present rejection.

A Reason to Make Specific Molecular Modifications to a Lead Compound is Required But Has Not Been Established

The Office also has not shown that the art would have suggested making the proposed modifications to the Moore Compound. Rather than showing that the art would have suggested the proposed modifications to the Moore Compound, the Office asserts that the differences between the Moore Compound and those of the present claims "can be **remedied** by the teaching of Lohmann". Office Action at 7 (emphasis added). Not only does that statement evidence the Office's use of impermissible hindsight, but also of an improper obviousness analysis. Specifically, in a proper obviousness analysis, "the question under 35 U.S.C. 103 is not whether the differences [between the art and the claims] themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." M.P.E.P. § 2141.02(I) (emphasis in original). In the present case, as detailed herein, the claimed invention as a whole would not have been obvious.

A showing that the art would have suggested making the proposed modifications to the Moore Compound is a requirement of a prima facie case of obviousness.

As explained in *Takeda,*

> [a] known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.' Id. We clarified, however, that **in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have**

> **suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required.**

Takeda Chemical Industries, Ltd., v. AlphaPharm Pty, Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).

In the present case, with respect to the proposed shift of the substituent at the 5-position of the Moore Compound to the 6-position, the Office simply notes that Lohmann teaches compositions having a substituent at the 6-position of a quinazoline ring. However, the Office makes no mention at all why that fact may have led one of ordinary skill in the art to shift the position of the substituent on the Moore Compound.

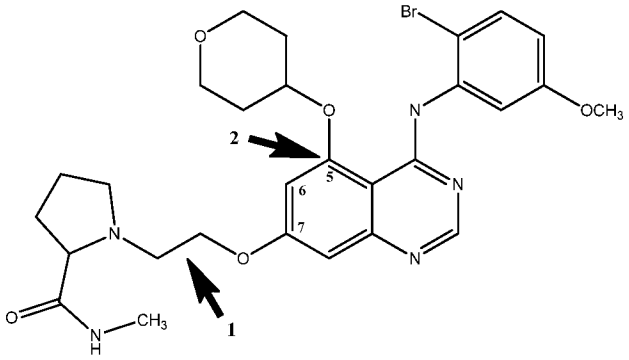
With respect to the proposed modification of Moore Compound's ethoxy linkage to form a direct -O- linkage, the Office merely alleges that one of ordinary skill in the art would have been motivated to make that modification "because [it] would have maintained the same biological activity for the compound as VEGF inhibitors." Office Action at 7. However, the Office provides no support at all for that bare assertion. And maintenance of biological activity, without more, would not have led one of ordinary skill in the art to make the proposed modification.

Accordingly, for at least the additional reason that the Office has not shown that the art would have suggested making either of the two proposed modifications to the Moore Compound, Applicants respectfully assert that a prima facie case of obviousness has not been established. Withdrawal of the present rejection is therefore requested.

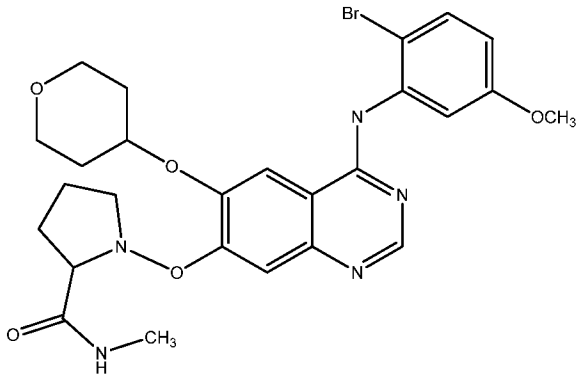
The Cited Art Would Not Have Suggested the Proposed Modifications of the Moore Compound

If the Moore Compound were modified in the manner proposed by the Office, the resulting compound, the "Modified Moore Compound," would not fall within Lohmann's disclosure. The Moore Compound and the Modified Moore Compound are shown below:

Moore Compound

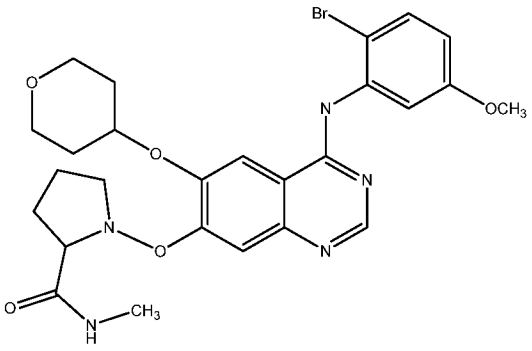


Modified Moore Compound

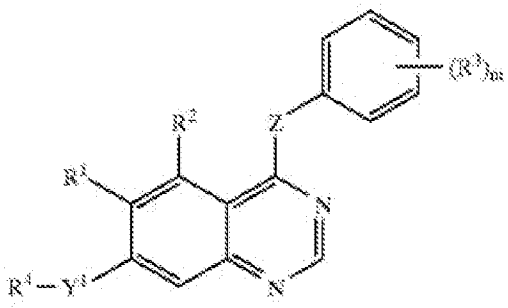


The Modified Moore Compound and Formula (I) of Lohmann are shown below:

Modified Moore Compound



Lohmann Formula (I)



For the Modified Moore Compound to fall within the scope of the Lohmann Formula (I):

- R^4-Y^1 would need to be 2-(N-methylcarbamoyl)pyrrolidin-1-yloxy;

- R^1 would need to be tetrahydropyran-4-yloxy;
- R^2 would need to be hydrogen;
- R^3 would need to be bromine and methoxy; and
- m would need to be 2.

However, as explained below, neither R^4-Y^1 nor R^1 in Lohmann is capable of being those groups.

For example, although in Lohmann Y^1 can be chosen from 10 classes of linking groups to be -O- and R^4 can be chosen from 8 classes of groups to be X^1, X^1 may not be <u>any</u> heterocyclic group as asserted by the Office, and may not, for example, be a pyrrolidinyl group.

Column 2 of Lohmann (cited by the Office and reproduced in the present Office Action) explains that X^1 represents a pyridone group, a phenyl group, or a 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S. Col. 2, ll. 51-53. A pyrrolidinyl group, which would be present in the Modified Moore Compound and required by the present claims, is not a pyridone group, a phenyl group, or a 5 or 6-membered *aromatic* heterocyclic group with 1 to 3 heteroatoms selected from O, N and S. Rather, a pyrrolidinyl group is a 5-membered *aliphatic* heterocyclic group with a N heteroatom.

Thus, in contrast to both the Modified Moore Compound and the present claims, the 7-position in Lohmann <u>cannot</u> be substituted with a pyrrolidinyl group bonded to the quinazoline ring by a linking group.

Similarly, R^1 at the 6-position of Lohmann <u>cannot</u> be a tetrahydropyranyloxy group, as it would be in the Modified Moore Compound.

Accordingly, if the Moore Compound were modified in the manner proposed by the Office, the resulting compound would not even fall within the scope of the compounds disclosed by Lohman. Thus, Lohmann would not only not suggest making the specific modifications of the Moore Compounds proposed by the Office, but would actually teach away from making those modifications.

For at least this additional reason, Applicants respectfully respectfully assert that a prima facie case of obviousness has not been established and request withdrawal of the present rejection.

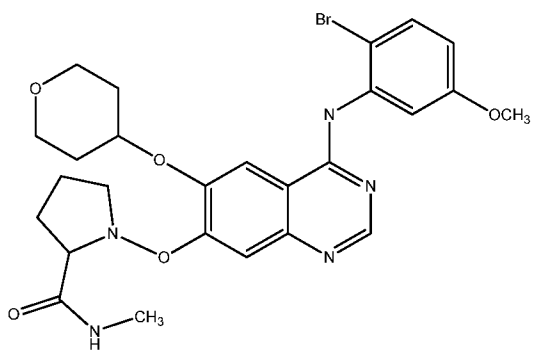
The Modified Moore Compound Would Not Meet All of the Limitations of the Present Claims

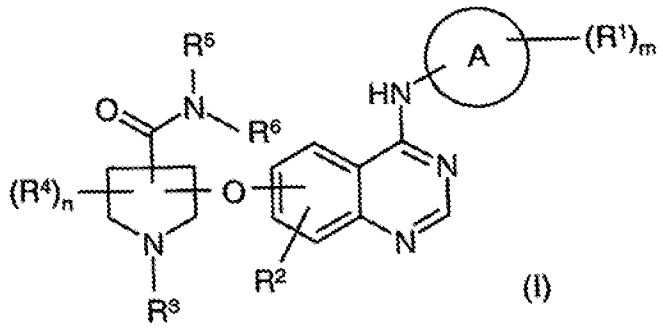
Not only would the Modified Moore Compound not fall within the scope of the Lohmann teachings, but it also would not meet all of the limitations of the present claims.

One of the fundamental requirements of a prima facie case of obviousness is that the art, when combined or modified, must teach or suggest all of the claim limitations. *See, e.g.,* M.P.E.P. § 2143. In the present case, that requirement has not been satisfied. Specifically, the Modified Moore Compound would not fall within the scope of the present claims.

The Modified Moore Compound and Formula (I) of the present claims are shown below:

Modified Moore Compound **Formula (I) of Present Claims**





For the Modified Moore Compound to fall within the scope of Formula (I) of the present claims:

- one of R^5 and R^6 would need to be methyl and the other hydrogen;
- R^4 would need to be hydrogen;
- R^3 would need to merge with the -O- linking group or be absent;
- R^2 would need to be tetrahydropyran-4-yloxy;
- A would need to be phenyl;
- R^1 would need to be bromine and methoxy; and
- m would need to be 2.

However, neither R^3 nor R^2 in the present claims is capable of being those groups.

For example, in the presently claimed compounds, R^2 cannot be a tetrahydropyranyloxy group, as it would be in the Modified Moore Compound. *See, e.g.,* claim 1. Similarly, the pyrrolidinyl ring of the presently claimed compounds cannot be bonded to the -O- linking group at the ring nitrogen, as it would be in the Modified Moore Compound. *Id.*

Accordingly, even if the Moore Compound were modified as proposed by the Office, it still would not fall within the scope of the present claims. For that additional reason, Applicants respectfully request withdrawal of the present rejection.

In summary, the Office has not provided a single reason why one of ordinary skill would have selected the Moore Compound as a lead compound for modification. The Office also has not shown that the art would have suggested making either of the two proposed modifications to the Moore Compound. The art, in fact, would not have suggested making either of those modifications but rather would have taught away from doing so. Finally, even if the Moore Compound were modified in the manner proposed by the Office, the modified compound still would not meet all of the limitations of the present claims. Accordingly, Applicants respectfully respectfully assert that a prima facie case of obviousness has not been established and request withdrawal of the present rejection.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account 50-3231.

Respectfully submitted,

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